Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 9-16, and 21 are pending in the application, with claim 9 being the sole independent claim. Claims 9 and 12-13 have been amended to more clearly and precisely define the subject matter which Applicants regard as the invention. Claims 17-20 and 22 have been canceled without prejudice to or disclaimer of the subject matter therein. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 9-22 under 35 U.S.C. § 112, first paragraph, because the specification "while enabling for the constructs of Figure 1" allegedly "does not reasonably provide enablement for all constructs comprising a deletion, insertion, or substitution in respect to all or part of a 3' untranslated region." Paper No. 8, page 3. Applicants respectfully traverse the rejection.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Some experimentation is permitted so long as the experimentation necessary to practice the invention is not undue. *In re Angstadt,* 537 F.2d 498, 504 (CCPA 1976).

The present invention establishes, *inter alia*, the principle that the addition of a nucleic acid encoding a signal peptide sequence to an mRNA encoding an intracellular protein is not sufficient

to target that mRNA to the endoplasmic reticulum (ER). In fact, as established by Applicants' disclosure, it is also necessary to modify and/or replace the native 3'UTR of the mRNA encoding the intracellular protein in order to remove any naturally-occurring signals which may affect or compete with the directing ability and efficiency of the signal peptide sequence. Accordingly, claim 9 is directed to a nucleic acid which allows a non-secreted protein to be synthesized in the ER (from where it can be secreted) and not in "an intracellular location other than the endoplasmic reticulum or . . . free and/or cytoskeletal bound polysomes." *See* claim 9. Thus, contrary to the Examiner's assertion that "Applicants desire nucleic acid molecules in which can be targeted to the ER, *FP, or CBPs*," (emphasis added) the claimed invention envisions *targeting* to only the ER.

In support of the rejection, the Examiner has asserted that "breadth of the claims is extensive with respect to all or part of a 3' untranslated region." Paper No. 8, page 3. The Examiner has further asserted that "Applicants do not provide enough guidance or working examples of nucleic acid constructs comprising a deletion, insertion, or substitution in respect to all or part of a 3' untranslated region" and "since the 3'-untranslated region is critical for targeting, it would be necessary to know the effect that a mutation in this region has on this targeting." *Id.* From the Examiner's objections, it is clear that the objection extends only to the portion of the 3'UTR to be deleted, inserted, or substituted. Applicants assert that the specification clearly enables one of ordinary skill in the art to delete, insert or substitute the whole of a 3'-UTR.

Specifically, the Examiner believes that "[i]t is not predictable to one of ordinary skill in the art what these critical nucleic acid residues in the 3'-untranslated region are which allow the targeting of these molecules to the desired locations in the cell." *Id.* Applicants respectfully disagree. As is clear from the specification, the invention is concerned with altering or removing the native 3'UTR of the non-secreted protein so that its effect in intracellular targeting is negated and the heterologous

signal peptide can direct synthesis in the ER. *See* Specification, page 4, lines 8-19. Therefore, one of ordinary skill in the art, need not know which residues "allow the targeting of these molecules to the desired locations in the cell." One of ordinary skill in the art need only know whether the 3'UTR has been sufficiently disrupted to negate its intracellular targeting effect. As described on page 4, lines 15-19 and in the examples, this can be determined without undue experimentation using a reporter gene and hybridization assays. Routine experimentation does not vitiate enablement of the claims. *In re Wands*, 8 USPQ2d 1400, 1404 (1988).

The disruption of the native 3'UTR such that its effect in intracellular targeting is negated can be considered to be similar to the disruption of cell-or temporal-specific promoter regions. If the promoter region is to be disrupted, one of ordinary skill in the art would simply carry out routine experiments in which the promoter region has insertions, substitutions or, most likely, deletions in order to obtain disruption. One of ordinary skill in the art would not be interested in which specific nucleic acid residues provide the specific activity of the promoter. Rather, one of ordinary skill in the art would be interested in providing a modified version of the promoter which does not have the native activity.

In view of the above, Applicants assert that claims are enabled and, therefore, respectfully request that the Examiner reconsider and withdraw the rejections.

The Examiner has also rejected claims 17-20 and 22 under 35 U.S.C. § 112, first paragraph, as allegedly not enabled by the specification. Paper No. 8, page 3. Solely to advance prosecution and not in acquiescence to the Examiner's rejection, Applicants have canceled claims 17-20 and 22. Accordingly, the Examiner's rejection is rendered moot and Applicants respectfully request that the rejection be withdrawn.

The Examiner has rejected claims under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. Paper No. 8, page 4. The Examiner, however, has not indicated specifically which claims are under rejection. From the Examiner's comments on page 5 of the Office Action, it appears that the rejection was intended to apply to claim 9.

Applicants assert that once the principle has been disclosed that the addition of a signal sequence to an mRNA encoding an intracellular protein and disruption of the native 3'UTR is necessary to target that mRNA efficiently into the endoplasmic reticulum, the skilled person would not have difficulty in contemplating the whole genus encompassed by the claims. Thus, Applicants assert that Applicants were in possession of the claimed genus when the application was filed. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner has also rejected claims 17-20 and 22 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. Paper No. 8, page 4. Solely to advance prosecution and not in acquiescence to the Examiner's rejection, Applicants have canceled claims 17-20 and 22. Accordingly, the Examiner's rejection is rendered moot and Applicants respectfully request that the rejection be withdrawn.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 9-22 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Paper No. 8, page 5. Specifically, the Examiner has opined that:

> Claim 9 is confusing since the claim does not recite that the nucleic acid molecule is isolated and purified. Therefore, the claims read on any cell which endogenously comprises these molecules.

Id. Applicants respectfully disagree with the Examiner. It is impossible for claim 9 to read on any cell which "endogenously comprises" a molecule as defined in claim 9. It is self-evident that no cell will comprise a nucleic acid which encodes the signal peptide sequence of a *secreted* protein operatively linked to a nucleic acid encoding a *non-secreted* protein. Thus, Applicants assert that the claim does not read on any cell which endogenously comprises these molecules. Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner has also rejected claims 9, 12, 13, 17-20 and 22 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Paper No. 8, page 6. Applicants respectfully traverse the Examiner's rejections.

Claims 9, 12, and 13 have been amended. Applicants believe the amendments clarify the subject matter of the claims. Thus, Applicants respectfully request that the Examiner reconsider and withdraw the rejection. Claims 17-20 and 22 have been deleted. Thus, the Examiner's rejection is rendered moot and Applicants respectfully request that the Examiner withdraw the rejection.

Claim Rejections Under 35 U.S.C. § 103

The Examiner has rejected claims 9-15 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Lee *et al.*, *Mol. Cells* 6: 552-56 (1996) in view of Hesketh *et al.*, *Biochem J.* 298:143-48 (1994). For the following reasons, Applicants respectfully disagree.

Initially, Applicants note that contrary to the Examiner's suggestion, the claims are not directed to a nucleic acid molecule "which has an altered 3' UTR which directs the molecule to the ER, FP or CBP." As discussed above, the present invention is concerned with directing mRNA encoding a non-secreted protein *to the ER* so that the protein will be secreted.

The Examiner alleges that Hesketh *et al.* makes it obvious to modify the coding sequences disclosed in Lee *et al.* by altering the 3' UTRs thereof so that they are more efficiently directed to *intracellular* locations. Again, Applicants note that the present invention is concerned with directing to the ER mRNAs which are not normally *directed to the ER*.

The present invention lies in the surprising and unexpected finding that, if an RNA encoding an intracellular protein is engineered to encode a signal peptide sequence (so that it will be secreted), the 3' UTR of the mRNA encoding the intracellular protein will compete with the signal sequence, said signal sequence trying to send the mRNA to the ER and the 3' UTR trying to send the mRNA elsewhere in the cell. Lee *et al.* relates to a protein which is naturally membrane-bound (sialyltransferase). Such a protein is, therefore, synthesized on membrane bound polysomes. Since the mRNA encoding this protein is naturally targeted to the ER, the 3'UTR thereof does not "try" to direct to the mRNA to another part of the cell. Accordingly, Lee *et al.* provide no motivation for one skilled in the art to alter the 3'UTR of the protein disclosed therein. Hesketh *et al.* teach that mRNAs encoding intracellular proteins can be localized by the 3'UTR sequences thereof. There is no disclosure or suggestion that modification of the 3'UTR can lead to secretion of the protein. There is also no suggestion in Hesketh *et al.* of retargeting mRNAs to allow secretion of an intracellular protein, nor is there any indication in this paper that there would be a need to modify or remove the 3'UTR to allow retargeting of an mRNA to the ER as a prerequisite for secretion.

Viewed in hindsight, it seems very simple that an mRNA encoding an intracellular protein can be engineered to allow secretion of the protein by adding a nucleic acid encoding signal peptide *and* removing or modifying the 3'UTR. However, at the priority date, one skilled in the art finds no motivation in the art to do this. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner has further rejected claims 9, 12, and 13 under 35 U.S.C. § 103(a) as allegedly unpatentable over Lee *et al.* in view of Hesketh *et al.* in further view of Maeda *et al.*, *Biochem. Mol. Biol. Int.* 42:825-32 (1997). Applicants respectfully traverse the Examiner's rejection.

The Examiner is correct that claim 13 should be read as specifying that the signal peptide sequence is from albumin, etc, and not that the protein secreted is albumin. However, as maintained above, this objection is moot as the subject matter of claim 9 is, we submit, novel and non-obvious.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

In the Title:

At page, the title:

Nucleic Acid Constructs Involved in the Regulation of Protein Secretion

In the claims:

9. (Once amended) A nucleic acid molecule encoding a mammalian signal peptide operatively linked to a nucleic acid encoding a protein that would normally not be secreted from a mammalian cell, said signal peptide allowing at least some of said protein to be synthesized on the endoplasmic reticulum in a manner so that said protein can be secreted, the nucleic acid molecule comprising a deletion, insertion, or substitution in respect [to]of all or part of a 3' untranslated region, relative to the corresponding region present in naturally occurring RNA encoding said protein, such that the region's effect in directing molecules to an intracellular location other than the endoplasmic reticulum or to free and/or cytoskeletal bound polysomes is eliminated or reduced relative to the corresponding naturally occurring sequence.

12. (Once amended) The nucleic acid molecule of claim 9, wherein said signal [sequence]peptide is a signal [sequence]peptide normally [associated with]from a protein which is secreted from mammalian cells.

13. (Once amended) The nucleic acid molecule of claim 12, wherein said protein which is secreted from mammalian cells is a growth hormone, a milk protein or albumin.

Claims 17-20 and 22 have been canceled.